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Dec. 3, 2004

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

Citizen Petition

We submit this petition under 21 CFR §10.30 and Federal Food, Drug, and Cosmetic Act Section 505)(b) and 505(j), 21 USC §§355 (b) and 355 (j).

A. Action Requested

FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (The Orange Book) cites Duragesic® as the reference listed drug (RLD) for fentanyl transdermal systems. Petitioner asks that FDA not approve any new or pending ANDA or application filed under Section 505)(b)(2) of the Act for a generic fentanyl transdermal product which is not supported by either

- clinical safety and efficacy studies for those products which have a controlled-release mechanism that differ from that for Duragesic® (Fentanyl Transdermal System) or
- more restrictive bioequivalence criterion than those currently used by FDA to evaluate controlled-release transdermal drug products which seek ANDA approval.

B. Statement of Grounds

1. Background on Fentanyl

Fentanyl is a Schedule II controlled opioid analgesic and interacts predominately with the opioid μ-receptor. These μ-binding sites are discretely distributed in the human brain, spinal cord, and other tissues.

In clinical settings, fentanyl

- exerts it principal pharmacologic effects on the central nervous system;
- may cause serious or life-threatening hypoventilation;
- may produce bradycardia;

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- may increase the patient's tolerance for pain and decrease the perception of suffering, although the presence of the pain itself may still be recognized;
- may cause orthostatic hypotension and fainting.

2. Duragesic® (Fentanyl Transdermal System)

Janssen Pharmaceutica Products, L.P. markets Duragesic®. According to the Janssen package insert:

> "Duragesic® is a transdermal system providing continuous systemic delivery of fentanyl, a potent opioid analgesic, for 72 hours. "
>
> "Duragesic® is a rectangular transparent unit comprising a protective liner and four functional layers. Proceeding from the outer surface toward the surface adhering to skin, there layers are: (1) a backing layer of polyester film; (2) a drug reservoir of fentanyl and alcohol USP gelled with hydroxyethyl cellulose; (3) an ethylene-vinyl acetate copolymer membrane that controls the rate of fentanyl delivery to the skin surface; and (4) a fentanyl containing silicon adhesive. Before use, a protective liner covering the adhesive layer is removed and discarded. "

3 Pharmacokinetics

Janssen's package insert states that

> "Duragesic® (fentanyl transdermal system) releases fentanyl from the reservoir at a nearly constant amount per unit of time. The concentration gradient existing between the saturated solution of drug in the reservoir and the lower concentration in the skin drives drug release. Fentanyl moves in the direction of the lower concentration at a rate determined by the copolymer release membrane and the diffusion of fentanyl through the skin layers."
>
> "Following Duragesic® application, the skin under the system absorbs fentanyl, and a depot of fentany concentrates in the upper skin layers. Fentanyl then becomes available to the systemic circulation. Serum fentanyl concentrations increase gradually following initial Duragesic® application, generally leveling off between 12 and 24 hours and remaining relatively constant, with some fluctuation, for the remainder of the 72 hour application period. Peak serum concentrations of fentanyl generally occurred between 24 and 72 hours after initial application. Serum fentanly concentrations achieved are proportional to the Duragesic® delivery rate."
>
> "After system removal, serum fentanyl concentrations decline gradually, falling about 50% in approximately 17 (range 13-22) hours."

4. Safety and Efficacy Concerns

The characteristics of the skin are not uniform from individual to individual. If there is significant variation in skin permeability among individuals, that variation may be reflected in differences in rates of absorption of drugs like fentanyl through the skin. For patients with high skin permeability, the skin would offer less resistance. In such a situation, the rate of drug absorption from the adhesive layer would increase giving rise to potential fentanyl overdose.

The Duragesic® transdermal system has a rate-controlling membrane layer which provides an upper limit on the rate at which fentanyl can be released from the reservoir into the skin. This membrane therefore acts as a safety mechanism for preventing delivery of this potent opioid at too high a rate

The importance of this safeguard should not be underestimated in the management of pain and potential hypoventilation. The safety of a product without a rate-controlled barrier cannot simply be assumed to be the same as that of the Duragesic® transdermal system.

5. Proposed Bioequivalence Requirements

Because fentanyl is a potent Schedule II opioid analgesic with an overdose potential for serious or life-threatening hypoventilation, the bioequivalence (BE) criterion for a generic Duragesic® transdermal system should be different than those commonly utilized for controlled-release generic transdermal drug products. The following requirements should be considered:

- The generic product should have "sameness" in the rate controlled-release mechanism as the Duragesic® transdermal system from a design aspect to ensure a safe delivery rate of fentanyl to the systemic circulation. If the delivery system design does not have the "sameness" in the rate controlled-release mechanism as in Duragesic® transdermal system, clinical safety and efficacy studies should be required.

- If the delivery system design does have the "sameness" in the rate controlled-release mechanism as in Duragesic® transdermal system:

    - The partial AUC up to median Tmax of the brand as an estimate of the absorption phase of the test formulation should be equivalent (90% Confidence Interval (CI) to be within 80%-125%) to that of the RLD in order to ensure that the rate of absorption of this potent opioid is not a safety concern.

    - The BE limits for Cmax and AUC should be contained within 90%-111% for 90% CI or contained within 80%-125% for 95% CI. This restrictive BE requirement is necessary because of the potency of fentanyl since any

significant change in plasma levels may have serious or life-threatening clinical consequences.

C. Conclusion

In view of safety concern associated with this potent Schedule II controlled substance (fentanyl), any generic transdermal system that lacks "sameness" in the controlled-release mechanism as to Duragesic® transdermal system should not be approved without clinical trials to demonstrate that the delivery mechanism is safe and efficacious and is comparable to those of Duragesic® transdermal system.

For those transdermal systems which have "sameness" in the controlled-release mechanism as in Duragesic® transdermal system, the BE limits for both Cmax and AUC parameters are either contained within 90%-111% for 90% CI or within 80%-125% for 95% CI. In addition, the 90% CI of the partial AUC up to median Tmax of the brand should be within 80%-125%.

D. Environmental Impact

The action requested in this citizen petition is exempt from the requirements for an Environmental Impact Statement or an Environmental Assessment under 21 C.F.R. §25.31.

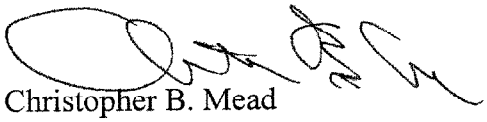
E. Economic Impact

An economic impact statement will be provided if requested.

F. Certification

The undersigned certifies that, to his best knowledge and belief, this petition includes all information and views on which the petitioner relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Sincerely,



Christopher B. Mead